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PGC-1α, a New Therapeutic Target in Huntington's Disease?

Jetta K. McGill[1] and M. Flint Beal[1,*]
[1]Department of Neurology, Cornell Medical Center, New York, NY 10021, USA
*Contact: fbeal@mail.med.cornell.edu
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The coactivator PGC-1α is a key regulator of mitochondrial biogenesis and respiration, mediating expression of several transcription factors required for these programs. Three new studies reveal that PGC-1α expression is downregulated in patients with Huntington's disease (HD) and in several animal models of this neurodegenerative disorder, implicating PGC-1α in HD pathogenesis and providing a connection between impaired energy metabolism and neurodegeneration (Cui et al., 2006; Weydt et al., 2006; St-Pierre et al., 2006).

Since its discovery a decade ago, PGC-1α (peroxisome proliferator-activated receptor-γ coactivator 1α) (Puigserver et al., 1998) has been implicated in energy homeostasis, adaptive thermogenesis, β-oxidation of fatty acids, and glucose metabolism (for review see Puigserver and Spiegelman, 2003). Originally identified as a PPAR-γ-interacting protein in brown adipose tissue, PGC-1α and its close homolog, PGC-1β, are highly expressed in tissues with increased energy demands and large numbers of mitochondria, including brown adipose tissue, heart muscle, and slow-twitch skeletal muscle (Puigserver et al., 1998). PGC-1α's ability to activate a diverse set of metabolic programs in different tissues depends on its ability to form heteromeric complexes with a variety of transcription factors including NRF-1 and NRF-2 and the nuclear hormone receptors PPARα, PPARδ, ERRα, and TR (for review see Lin et al., 2005). Of particular interest are NRF-1, NRF-2, and ERRα, given that they regulate the expression of many nuclear-encoded mitochondrial genes including those encoding cytochrome *c*, complexes I–V, and mitochondrial transcription factor A (Tfam) (for review see Kelly and Scarpulla, 2004). Three new studies—two in *Cell* (Cui et al., 2006; St-Pierre et al., 2006) and one in *Cell Metabolism* (Weydt et al., 2006)—now implicate loss of PGC-1α function in the neurodegenerative disorder Huntington's disease (HD).

HD is an autosomal-dominant disorder characterized by lesions in the striatum of the brain that cause progressive behavioral and cognitive impairments and involuntary choreiform movements. The genetic defect is caused by expansion of an unstable CAG repeat in the *huntingtin* gene resulting in a greatly expanded polyglutamine tract in the protein it encodes. How the mutant huntingtin protein elicits its toxic effects is unclear, but several mechanisms have been postulated including transcriptional dysregulation, abnormalities in energy metabolism, and oxidative damage (reviewed in Browne and Beal, 2004).

One of the first indications that bioenergetic defects might be implicated in HD pathogenesis came from the finding that HD patients display pronounced weight loss, despite increased caloric intake. Imaging with positron emission tomography (PET) and nuclear magnetic resonance (NMR) spectroscopy revealed a marked reduction in glucose metabolism and an increase in lactate, respectively, in the basal ganglia of HD patients. In addition, biochemical studies revealed reduced activity of several key components of oxidative phosphorylation, including complexes II, III, and IV of the electron transport chain in mitochondria of striatal neurons in HD patients at an advanced stage of disease (reviewed in Browne and Beal, 2004). Studies on lymphoblasts from HD patients revealed other mitochondrial abnormalities including a decreased membrane resting potential, impaired calcium ion homeostasis (Panov et al., 2002), and marked morphological abnormalities including derangement of the mitochondrial matrix and cristae (Squitieri et al., 2006). This appears to be a direct effect of mutant huntingtin, given that these mitochondrial abnormalities can be recapitulated in normal lymphoblasts treated with a fusion protein composed of a peptide containing a pathogenic polyglutamine tract (Panov et al., 2002). Indeed, there is evidence from an HD mouse model (YAC72) and from cultured HD striatal neurons expressing endogenous mutant huntingtin ($STHdh^{Q111}$) that this mutant protein associates directly with the outer mitochondrial membrane (Choo et al., 2004). The $STHdh^{Q111}$ cultured cell line also displayed reduced rates of oxygen consumption and ATP production (Milakovic and Johnson, 2005) and increased sensitivity to 3-nitropropionic acid (3-NP) (Gines et al., 2003), a complex II inhibitor capable of inducing HD-like symptoms in many different species. The molecular basis of these mitochondrial defects in HD remains unclear. It has been proposed that aberrant transcriptional regulation of nuclear-encoded mitochondrial genes may be involved in HD pathogenesis. Indeed, mutant huntingtin binds to several key transcription fac-

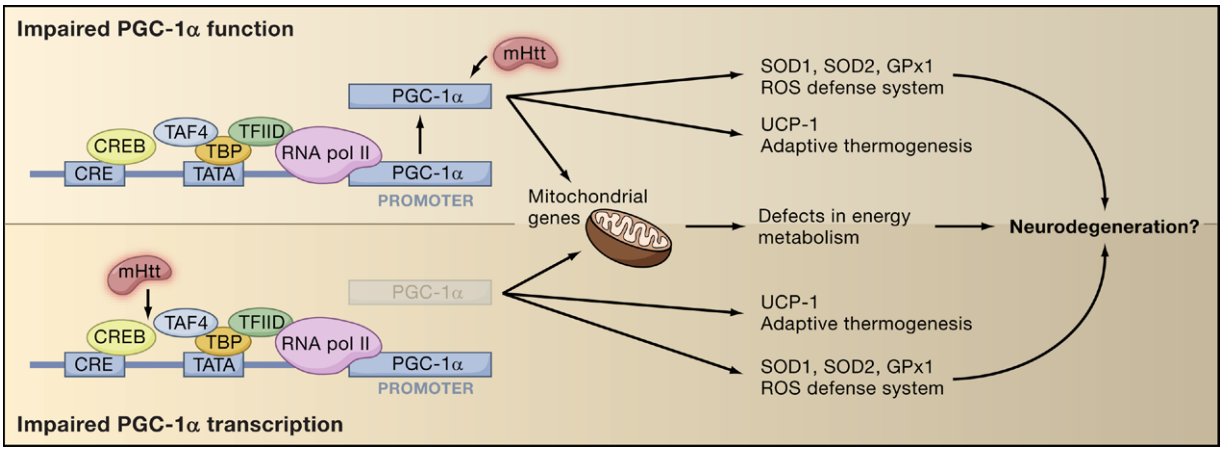

Figure 1. Mechanisms by which Mutant Huntingtin Impairs PGC-1α Function in HD Pathogenesis

(Top) In Huntington's disease (HD), Weydt et al. (2006) show that the mutant huntingtin (mHtt) protein impairs the ability of PGC-1α to switch on downstream target genes such as the gene encoding UCP-1 in brown adipose tissue. Although there is no direct evidence that mHtt binds directly to PGC-1α, mHtt does block PGC-1α's function as a coactivator. (Bottom) Cui et al. (2006) show that association of mHtt with the CREB/TAF4 complex on the PGC-1α promoter impairs PGC-1α activity by blocking transcription of its gene. These two models for how mHtt may regulate PGC-1α activity are not mutually exclusive because mHtt could have different modes of action depending on the tissue. Impairment of PGC-1α function and downregulation of its mitochondrial target genes could lead to abnormalities in mitochondrial function and energy metabolism, contributing to neurodegeneration in susceptible neurons (Cui et al., 2006; Weydt et al., 2006). Meanwhile impaired PGC-1α transcription and activity impact the enzyme system that combats reactive oxygen species (ROS). This leads to downregulation of ROS defense genes encoding, for example, SOD1, SOD2, and glutathione peroxidase (GPx1), resulting in increased oxidative damage and neuronal death (St-Pierre et al., 2006).

tors—including Sp1, TAFII130, and CREB binding protein (reviewed in Sugars and Rubinsztein, 2003)—and downregulates their activity. The three new studies in *Cell* and *Cell Metabolism* tie together these disparate strands of information, implicating mutant huntingtin in the dysregulation of PGC-1α transcription and activity, impaired mitochondrial function, and HD pathogenesis (Cui et al., 2006; St-Pierre et al., 2006; Weydt et al., 2006).

Initial interest that PGC-1α might play a role in HD pathogenesis came from studies on mice lacking PGC-1α (Lin et al., 2004; Leone et al., 2005). These mice display a profound spongiform pattern of lesions in the central nervous system, predominantly in the striatum, and exhibit abnormalities in brown adipose tissue. In addition, mice lacking PGC-1α display impaired thermoregulation, marked hyperactivity, and frequent limb clasping. Neurodegeneration predominantly in the striatum together with hyperactivity are features reminiscent of HD in humans, potentially implicating PGC-1α in the selective vulnerability of striatal neurons in HD. But what is the mechanism underpinning this selective vulnerability? One possibility is increased oxidative stress.

In their new study in *Cell*, St-Pierre et al. (2006) provide evidence that PGC-1α is a potent suppressor of reactive oxygen species (ROS) and induces production of ROS scavenging enzymes. They show that in response to treatment with the oxidative stressor, hydrogen peroxide, there is a ~6-fold increase in PGC-1α expression levels (and those of the related factor, PGC-1β) in a mouse embryonic fibroblast cell line. Concomitantly, there is increased expression of genes encoding ROS defense enzymes, including copper/zinc superoxide dismutase (SOD1), manganese SOD (SOD2), catalase, and glutathione peroxidase. To definitively determine the role of PGC-1α in the regulation of ROS defense enzymes, the authors infected the mouse embryonic fibroblast cell line with an adenovirus encoding a small inhibitory RNA (RNAi) against PGC-1α. When these RNAi-treated cells were exposed to hydrogen peroxide, they exhibited reduced expression of genes encoding PGC-1α and the ROS defense system (including SOD1, SOD2, and glutathione peroxidase). Analysis of mice lacking PGC-1α revealed that the basal expression of SOD1, SOD2, and catalase is considerably lower in the heart and brain, regions known to be very sensitive to oxidative stress. St-Pierre et al. (2006) also provide evidence that the master transcription factor CREB is important in the regulation of PGC-1α activity in response to hydrogen peroxide treatment. CREB is known to be an important regulator of PGC-1α expression under normal physiological conditions (Herzig et al., 2001; Handschin et al., 2003). St-Pierre et al. (2006) now show that PGC-1α-deficient mice are more sensitive to the effects of two neurotoxins—MPTP, a complex I inhibitor that targets the substantia nigra, and kainic acid, a glutamate receptor agonist that induces excitotoxicity in the hippocampus—exhibiting increased apoptosis of neurons and oxidative damage in the brain. As the authors point out, however, it is not yet possible to conclude that a lack of PGC-1α is the cause of the more pronounced neurodegeneration in the knockout mice compared to control animals treated with the two neurotoxins. However, it does seem likely that loss of PGC-1α enhances neurodegeneration in response to these neurotoxins, particularly given that

MPTP, which induces parkinsonian symptoms in mice and nonhuman primates, is known to cause oxidative damage and mitochondrial dysfunction.

In their new work, Cui et al. (2006) and Weydt et al. (2006) address separately the specific role of PGC-1α in mitochondrial dysfunction and HD pathogenesis. Cui et al. (2006) use three different sources of striatal neurons for their experiments: striata from postmortem HD patient brains, striata from an HD knockin mouse model that overexpresses mutant huntingtin, and the STHdh^{Q111} cultured HD striatal cell line. The authors report a marked reduction in the expression of PGC-1α mRNA in these three sources of striatal neurons and suggest that mutant huntingtin interferes with formation of the CREB/TAF4 complex that regulates transcription of the gene encoding PGC-1α (see Figure 1). In addition, the STHdh^{Q111} striatal neuronal line exhibited reduced expression of known mitochondrial gene targets of PGC-1α, including cytochrome *c* and cytochrome oxidase IV. Of particular interest, in knockin HD mice (with 140 CAG repeats inserted into the murine *huntingtin* gene), the expression of PGC-1α was reduced several-fold in medium spiny neurons but increased almost 50-fold in nNOS interneurons. This suggests that the selective vulnerability of medium spiny neurons and the resistance of interneurons (which are spared in HD) may be a consequence of altered PGC-1α expression. An important question is whether overexpression of PGC-1α is neuroprotective? A lentiviral vector expressing PGC-1α administered directly to the striatum of the R6/2 HD mouse model (in which about 150 CAG repeats are expressed in an N-terminal fragment of the mutant *huntingtin* gene) induced a marked increase in mean neuronal volume. This indicates that PGC-1α overexpression may prevent neuronal atrophy in these animals. A key question, which Cui et al. (2006) do not address, is whether overexpression of PGC-1α results in improved survival or motor performance in the R6/2 HD mice. Future experiments are needed to confirm whether PGC-1α is neuroprotective. However, the authors do show that downregulation of PGC-1α worsens behavioral and neuropathological abnormalities in a PGC-1α knockout/HD knockin mouse model (PGC-1α KO/KI). The knockin HD mouse has a relatively mild phenotype (Menalled et al., 2003), whereas the PGC-1α KO/KI animals display marked worsening of motor performance and reductions in striatal neuronal volume at 6 months of age compared to their PGC-1α knockout or HD knockin littermates. Moreover, these KO/KI mice are more susceptible to the neurotoxic effects of 3-NP, which is not surprising given that oxidative stress is important in 3-NP-mediated neurotoxicity and that PGC-1α regulates the production of antioxidant enzymes. Cui et al. (2006) further show that mutant huntingtin interferes with the ability of CREB/TAF4 to bind to the *PGC-1α* promoter and to induce transcription of the *PGC-1α* gene (see Figure 1).

In a related study, Weydt et al. (2006) provide further evidence of impaired PGC-1α function in HD. Using microarray expression data from the caudate nucleus of HD patient postmortem brain tissue, the authors report reduced expression of 24 out of 26 PGC-1α target genes. Similar to the Cui et al. (2006) findings, Weydt et al. (2006) report reduced PGC-1α mRNA expression in the striatum of N171-82Q HD mice. Collectively, these data support a role for interference with PGC-1α transcription in the striatal neurodegeneration characteristic of HD.

Expression of PGC-1α is rapidly induced in response to cold, and this coactivator regulates expression of key components of adaptive thermogenesis including UCP-1, which uncouples respiration resulting in heat production in brown adipose tissue. Weydt et al. (2006) report marked hypothermia at baseline temperatures and following cold exposure in both the N171-82Q and R6/2 HD mouse models. Following cold exposure, UCP-1 expression is decreased in brown adipose tissue from N171-82Q HD mice relative to wild-type animals, implicating impaired PGC-1α function in these mice. Failure to induce expression of the *UCP-1* gene and other PGC-1α target genes is further demonstrated in pre-adipocyte cells and in primary brown adipocytes from N171-82Q mice. In these animals, there is evidence for a reduced ATP/ADP ratio and reduced numbers of mitochondria in their adipocytes, as well as abnormal brown adipose tissue, similar to the findings in PGC-1α-deficient mice (Lin et al., 2004). The finding that UCP-1 expression but not PGC-1α expression is reduced suggests an alternative way in which mutant huntingtin could affect the function of PGC-1α. Cui et al. (2006) propose that mutant huntingtin may interfere with the transcription of PGC-1α, whereas Weydt et al. (2006) suggest that mutant huntingtin may bind to PGC-1α, impairing its ability to upregulate expression of its downstream target genes including UCP-1 in brown adipose tissue (see Figure 1).

The three new studies implicate PGC-1α as an important mediator in protecting neurons against oxidative damage, and its loss of function may contribute to HD pathogenesis. However, to definitively demonstrate that PGC-1α is involved in HD pathogenesis will require crossing a mouse overexpressing a brain-specific form of PGC-1α with an HD mouse strain. The resulting offspring should provide important information on both the functional and neuroprotective effects of PGC-1α in HD pathogenesis. The finding that PGC-1α expression is impaired in the striatum of HD patients raises the possibility that molecules that activate PGC-1α may be therapeutically useful. Such molecules are already in development because reduced PGC-1α expression has been strongly implicated in obesity and type II diabetes, which are major health problems (Puigserver and Spiegelman, 2003). These therapeutic agents may be valuable for treating HD as well as other neurodegenerative diseases in which mitochondrial dysfunction and oxidative damage play an important pathogenic role, such as Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis (reviewed in Lin and Beal, 2006).

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